

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use APRETUDE safely and effectively. See full prescribing information for APRETUDE.

APRETUDE (cabotegravir extended-release injectable suspension), for intramuscular use
Initial U.S. Approval: 2021

WARNING: RISK OF DRUG RESISTANCE WITH USE OF APRETUDE FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED HIV-1 INFECTION

See full prescribing information for complete boxed warning.

Individuals must be tested for HIV-1 infection prior to initiating APRETUDE or oral cabotegravir, and with each subsequent injection of APRETUDE, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Drug-resistant HIV-1 variants have been identified with use of APRETUDE for HIV-1 PrEP by individuals with undiagnosed HIV-1 infection. Do not initiate APRETUDE for HIV-1 PrEP unless negative infection status is confirmed. Individuals who become infected with HIV-1 while receiving APRETUDE for PrEP must transition to a complete HIV-1 treatment regimen. (2.2, 4, 5.1)

INDICATIONS AND USAGE

APRETUDE is an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating APRETUDE (with or without an oral lead-in with oral cabotegravir) for HIV-1 PrEP. (1)

DOSAGE AND ADMINISTRATION

- HIV-1 Screening: Screen all individuals for HIV-1 infection immediately prior to initiating APRETUDE for HIV-1 PrEP and prior to each injection while taking APRETUDE. (2.2)
- Prior to initiating APRETUDE, an oral lead-in dosing may be used for approximately 1 month with the recommended dosage to assess the tolerability of APRETUDE. (2.4)
- For gluteal intramuscular injection only. (2.5, 2.6)
- Recommended Dosing Schedule: Initiate APRETUDE with a single 600 mg (3-mL) injection given 1 month apart for 2 consecutive months on the last day of an oral lead-in if used or within 3 days and continue with the injections every 2 months thereafter. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection: Single-dose vial of 600 mg/3 mL (200 mg/mL) of cabotegravir extended-release injectable suspension. (3)

CONTRAINDICATIONS

- Unknown or positive HIV-1 status. (4)
- Previous hypersensitivity reaction to cabotegravir. (4)
- Coadministration with drugs where significant decreases in cabotegravir plasma concentrations may occur. (4)

WARNINGS AND PRECAUTIONS

- Comprehensive management to reduce the risk of HIV-1 acquisition. (5.1)
- Potential risk of developing resistance to APRETUDE if an individual acquires HIV-1 either before or while taking APRETUDE or following discontinuation of APRETUDE. Reassess risk of HIV-1 acquisition and test before each injection to confirm HIV-1 negative status. (5.2)
- Residual concentrations of cabotegravir may remain in the systemic circulation of individuals up to 12 months or longer. (5.3)
- Hypersensitivity reactions have been reported in association with other integrase inhibitors.

- Discontinue APRETUDE immediately if signs or symptoms of hypersensitivity reactions develop. (5.4)
- Hepatotoxicity has been reported in patients receiving cabotegravir. Clinical and laboratory monitoring should be considered. Discontinue APRETUDE if hepatotoxicity is suspected. (5.5)
 - Depressive disorders have been reported with APRETUDE. Prompt evaluation is recommended for depressive symptoms. (5.6)

ADVERSE REACTIONS

The most common adverse reactions (all grades) observed in at least 1% of subjects receiving APRETUDE were injection site reactions, diarrhea, headache, pyrexia, fatigue, sleep disorders, nausea, dizziness, flatulence, abdominal pain, vomiting, myalgia, rash, decreased appetite, somnolence, back pain, and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with APRETUDE. (4, 5.7, 7)
- Drugs that induce uridine diphosphate glucuronosyltransferase (UGT1A1) may significantly decrease plasma concentrations of cabotegravir. (4, 7.2, 7.3)

USE IN SPECIFIC POPULATIONS

- Lactation: Assess the benefit-risk of using APRETUDE to the infant while breastfeeding due to the potential for adverse reactions and residual concentrations in the systemic circulation for up to 12 months or longer after discontinuation. (8.2)
- Pediatrics: Not recommended in individuals weighing <35 kg. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosage and Administration Overview
- 2.2 HIV-1 Screening for Individuals Receiving APRETUDE for HIV-1 PrEP
- 2.3 Adherence to APRETUDE
- 2.4 Optional Oral Lead-in Dosing to Assess Tolerability of APRETUDE
- 2.5 Gluteal Intramuscular Injection Dosing with APRETUDE
- 2.6 Recommended Dosing Schedule for Missed Injections
- 2.7 Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Comprehensive Management to Reduce the Risk of HIV-1 Infection
- 5.2 Potential Risk of Resistance with APRETUDE
- 5.3 Long-Acting Properties and Potential Associated Risks with APRETUDE
- 5.4 Hypersensitivity Reactions
- 5.5 Hepatotoxicity
- 5.6 Depressive Disorders
- 5.7 Risk of Reduced Drug Concentration of APRETUDE Due to Drug Interactions

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Use of Other Antiretroviral Drugs after Discontinuation of APRETUDE
- 7.2 Potential for Other Drugs to Affect APRETUDE
- 7.3 Established and Other Potentially Significant Drug Interactions
- 7.4 Drugs without Clinically Significant Interactions with Cabotegravir

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Clinical Trials in Adults for HIV-1 Pre-Exposure Prophylaxis

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF DRUG RESISTANCE WITH USE OF APRETUDE FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED HIV-1 INFECTION

Individuals must be tested for HIV-1 infection prior to initiating APRETUDE or oral cabotegravir, and with each subsequent injection of APRETUDE, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Drug-resistant HIV-1 variants have been identified with use of APRETUDE by individuals with undiagnosed HIV-1 infection. Do not initiate APRETUDE for HIV-1 PrEP unless negative infection status is confirmed. Individuals who become infected with HIV-1 while receiving APRETUDE for PrEP must transition to a complete HIV-1 treatment regimen [see *Dosage and Administration* (2.2), *Contraindications* (4), *Warnings and Precautions* (5.1)].

1 INDICATIONS AND USAGE

APRETUDE is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating APRETUDE (with or without an oral lead-in with oral cabotegravir) for HIV-1 PrEP [see *Dosage and Administration* (2.2, 2.4), *Contraindications* (4), *Warnings and Precautions* (5.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration Overview

- APRETUDE contains cabotegravir extended-release injectable suspension in a single-dose vial [see *Dosage Forms and Strengths* (3)].
- APRETUDE must be administered by a healthcare provider by gluteal intramuscular injection [see *Dosage and Administration* (2.7)].
- APRETUDE may be initiated with oral cabotegravir prior to the intramuscular injections or the patient may proceed directly to injection of APRETUDE without an oral lead-in [see *Dosage and Administration* (2.4)].

2.2 HIV-1 Screening for Individuals Receiving APRETUDE for HIV-1 PrEP

Individuals must be tested for HIV-1 infection prior to initiating APRETUDE or oral cabotegravir, and with each subsequent injection of APRETUDE, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. If an antigen/antibody-specific test is used and provides negative results, then such negative results should be confirmed using an RNA-specific assay, even if the results of the RNA-assay are available after APRETUDE or oral cabotegravir administration [see *Contraindications* (4), *Warnings and Precautions* (5.1)].

2.3 Adherence to APRETUDE

Prior to starting APRETUDE, healthcare providers should carefully select individuals who agree to the required injection dosing and testing schedule and counsel individuals about the importance of adherence to scheduled dosing visits to help reduce the risk of acquiring HIV-1 infection and development of resistance [see *Dosage and Administration* (2.1), *Warnings and Precautions* (5.1), *Microbiology* (12.4)].

2.4 Optional Oral Lead-in Dosing to Assess Tolerability of APRETUDE

The healthcare provider and individual may decide to use an oral lead-in with oral cabotegravir prior to the initiation of APRETUDE to assess the tolerability of cabotegravir or the healthcare provider and individual may proceed directly to injection of APRETUDE without the use of an oral lead-in [see *Dosage and Administration* (2.5)].

No safety and efficacy data are available for use of APRETUDE without an oral lead-in [see *Warnings and Precautions* (5.3), *Adverse Reactions* (6.1)]. However, in HIV-1 treatment clinical trials, data show that an oral lead-in is not needed to ensure adequate plasma cabotegravir exposure upon initiation of injections and that the safety and efficacy results of CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) were similar when administered with and without an oral lead-in.

2.5 Gluteal Intramuscular Injection Dosing with APRETUDE

Initiation Injections

If an oral lead-in is used, initiation injections should be administered on the last day of oral lead-in or within 3 days thereafter. The recommended initiation injection doses of APRETUDE in individuals is a single 600-mg (3-mL) intramuscular injection of APRETUDE given 1 month apart for 2 consecutive months (Table 1 and Table 2). Individuals may be given the second APRETUDE initiation injection up to 7 days before or after the date the individual is scheduled to receive the injections.

Continuation Injections

After the 2 initiation injection doses given consecutively 1 month apart, the recommended continuation injection dose of APRETUDE is a single 600-mg (3-mL) intramuscular injection of APRETUDE every 2 months (Table 2). Individuals may be given APRETUDE up to 7 days before or after the date the individual is scheduled to receive the injections.

Table 1. Recommended Dosing Schedule (with Oral Lead-in) for Pre-exposure Prophylaxis in Adults and Adolescents Weighing at Least 35 kg

Oral Lead-in (at Least 28 Days)	Intramuscular (Gluteal) Initiation Injection (Month 2 and Month 3)	Intramuscular (Gluteal) Continuation Injection (Month 5 and Every 2 Months Onwards)
Oral cabotegravir 30 mg by mouth once daily for 28 days	APRETUDE ^a 600 mg (3 mL)	APRETUDE ^b 600 mg (3 mL)

^a Should be administered on the last day of oral lead-in or within 3 days thereafter.

^b Individuals may be given APRETUDE up to 7 days before or after the date the individual is scheduled to receive the injections.

Table 2. Recommended Dosing Schedule (Direct to Injection) for Pre-exposure Prophylaxis in Adults and Adolescents Weighing at Least 35 kg

Intramuscular (Gluteal) Initiation Injection (Month 1 and Month 2)	Intramuscular (Gluteal) Continuation Injection (Month 4 and Every 2 Months Onwards)
APRETUDE ^a 600 mg (3 mL)	APRETUDE ^a 600 mg (3 mL)

^a Individuals may be given APRETUDE up to 7 days before or after the date the individual is scheduled to receive the injections.

2.6 Recommended Dosing Schedule for Missed Injections

Adherence to the injection dosing schedule is strongly recommended. Individuals who miss a scheduled injection visit should be clinically reassessed to ensure resumption of APRETUDE remains appropriate [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1, 5.2)]. Refer to Table 3 for dosing recommendations after missed injections.

Planned Missed Injections

If an individual plans to miss a scheduled every-2-month continuation injection visit by more than 7 days, take daily oral cabotegravir for a duration of up to 2 months to replace 1 missed scheduled every-2-month injection. The recommended oral daily dose is one 30-mg tablet of oral cabotegravir. The first dose of oral PrEP should be taken approximately 2 months after the last injection dose of APRETUDE. Restart injection with APRETUDE on the day oral dosing completes or within 3 days; thereafter, as recommended in Table 3. For oral PrEP durations greater than 2 months, an alternative oral regimen is recommended.

Unplanned Missed Injections

If a scheduled injection visit is missed or delayed by more than 7 days and oral dosing has not been taken in the interim, clinically reassess the individual to determine if resumption of injection dosing remains appropriate [see *Warnings and Precautions* (5.1)]. If the injection dosing schedule will be continued, see Table 3 for dosing recommendations.

Table 3. Injection Dosing Recommendations after Missed Injections

Time since Last Injection	Recommendation
If second injection is missed and time since first injection is:	
Less than or equal to 2 months	Administer 600-mg (3-mL) gluteal intramuscular injection of APRETUDE as soon as possible, then continue to follow the every-2-month injection dosing schedule.
Greater than 2 months	Restart with 600-mg (3-mL) gluteal intramuscular injection of APRETUDE, followed by a second 600-mg (3-mL) initiation injection dose 1 month later. Then continue to follow the every-2-month injection dosing schedule thereafter.
If third or subsequent injection is missed and time since prior injection is:	
Less than or equal to 3 months	Administer 600-mg (3-mL) intramuscular injection of APRETUDE as soon as possible, then continue with the every-2-month injection dosing schedule.
Greater than 3 months	Restart with 600-mg (3-mL) gluteal intramuscular injection of APRETUDE, followed by the second 600-mg (3-mL) initiation injection dose 1 month later. Then continue with the every-2-month injection dosing schedule thereafter.

2.7 Administration Instructions

Refer to the Instructions for Use for complete administration instructions with illustrations.

APRETUDE is a suspension for gluteal intramuscular injection that does not need further dilution or reconstitution.

The ventrogluteal site is recommended for injection. A dorsogluteal approach (upper outer quadrant) is acceptable, if preferred by the healthcare professional. Do not administer by any other route or anatomical site. Consider the body mass index (BMI) of the individual to ensure that the needle length is sufficient to reach the gluteus muscle. Longer needle lengths (not included in the dosing kit) may be required for individuals with higher BMI (e.g., $>30 \text{ kg/m}^2$) to ensure that the injection is administered intramuscularly as opposed to subcutaneously.

Store APRETUDE at 2°C to 25°C (36°F to 77°F) in the original carton until ready to use. Exposure up to 30°C (86°F) permitted. Do not freeze.

If the pack has been stored in the refrigerator, the vial should be brought to room temperature prior to administration (not to exceed 30°C [86°F]).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The APRETUDE vial has a brown tint to the glass that may limit visual inspection. Discard the vial if the medicine exhibits particulate matter or discoloration.

Shake the vial vigorously so that the suspension looks uniform before injecting. Small air bubbles are expected and acceptable.

Once the suspension has been drawn into the syringe, the injection should be administered as soon as possible, but may remain in the syringe for up to 2 hours. The filled syringe should not be placed in the refrigerator. If the medicine remains in the syringe for more than 2 hours, the filled syringe and needle must be discarded [see *How Supplied/Storage and Handling* (16)].

3 DOSAGE FORMS AND STRENGTHS

Injection: Single-dose vial containing 600 mg/3 mL (200 mg/mL) of cabotegravir as a white to light pink, free-flowing, extended-release injectable suspension.

4 CONTRAINDICATIONS

APRETUDE is contraindicated in individuals:

- with unknown or positive HIV-1 status [see *Warnings and Precautions* (5.1, 5.2)].
- with previous hypersensitivity reaction to cabotegravir [see *Warnings and Precautions* (5.4)].
- receiving the following coadministered drugs for which significant decreases in cabotegravir plasma concentrations may occur due to uridine diphosphate glucuronosyltransferase (UGT1A1) [see *Drug Interactions* (7.2, 7.3), *Clinical Pharmacology* (12.3)]:
 - o Anticonvulsants: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
 - o Antimycobacterials: Rifampin, rifapentine

5 WARNINGS AND PRECAUTIONS

5.1 Comprehensive Management to Reduce the Risk of HIV-1 Infection

Use APRETUDE for HIV-1 PrEP to reduce the risk of HIV-1 infection as part of a comprehensive prevention strategy including adherence to the administration schedule and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs). APRETUDE is not always effective in preventing HIV-1 acquisition [see *Clinical Studies (14.1)*]. The time from initiation of APRETUDE for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Risk for HIV-1 acquisition includes behavioral, biological, or epidemiologic factors including, but not limited to, condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high prevalence area or network.

Counsel individuals on the use of other prevention measures (e.g., consistent and correct condom use; knowledge of partner(s)' HIV-1 status, including viral suppression status; regular testing for STIs that can facilitate HIV-1 transmission). Inform individuals about and support their efforts in reducing sexual risk behavior.

Use APRETUDE to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-1 negative [see *Contraindications (4)*]. HIV-1 resistance substitutions may emerge in individuals with undiagnosed HIV-1 infection who are taking only APRETUDE, because APRETUDE alone does not constitute a complete regimen for HIV-1 treatment [see *Microbiology (12.4)*]; therefore, care should be taken to minimize the risk of initiating or continuing APRETUDE before confirming the individual is HIV-1 negative.

- Prior to initiating APRETUDE for HIV-1 PrEP, ask seronegative individuals about recent (in past month) potential exposure events (e.g., condomless sex or condom breaking during sex with a partner of unknown HIV-1 status or unknown viremic status, a recent STI), and evaluate for current or recent signs or symptoms consistent with acute HIV-1 infection (e.g., fever, fatigue, myalgia, skin rash).
- If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.

When using APRETUDE for HIV-1 PrEP, HIV-1 testing should be repeated prior to each injection and upon diagnosis of any other STIs [see *Dosage and Administration (2.2, 2.5)*].

- If an HIV-1 test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following an exposure event, additional HIV testing to determine HIV status is needed. If an individual has confirmed HIV-1 infection, then the individual must be transitioned to a complete HIV-1 treatment regimen.

Counsel HIV-1 uninfected individuals to strictly adhere to the recommended dosing and testing schedule for APRETUDE in order to reduce the risk of HIV-1 acquisition and the potential development of resistance [see *Dosage and Administration (2.3, 2.5)*, *Microbiology (12.4)*]. Some individuals, such as adolescents, may benefit from frequent visits and counseling to support adherence to the dosing and testing schedule [see *Use*

in Specific Populations (8.4), Microbiology (12.4), Clinical Studies (14)].

5.2 Potential Risk of Resistance with APRETUDE

There is a potential risk of developing resistance to APRETUDE if an individual acquires HIV-1 either before or while taking APRETUDE or following discontinuation of APRETUDE *[see Warnings and Precautions (5.1, 5.3)]*.

To minimize this risk, it is essential to clinically reassess individuals for risk of HIV-1 acquisition and to test before each injection to confirm HIV-1 negative status. Individuals who are confirmed to have HIV-1 infection must transition to a complete HIV-1 treatment regimen.

Alternative forms of PrEP should be considered following discontinuation of APRETUDE for those individuals at continuing risk of HIV-1 acquisition and initiated within 2 months of the final injection of APRETUDE.

5.3 Long-Acting Properties and Potential Associated Risks with APRETUDE

Residual concentrations of cabotegravir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer). It is important to carefully select individuals who agree to the required every-2-month injection dosing schedule because non-adherence to every-2-monthly injections or missed doses could lead to HIV-1 acquisition and development of resistance.

Healthcare providers should take the prolonged-release characteristics of cabotegravir into consideration when APRETUDE is prescribed *[see Dosage and Administration (2.3), Warnings and Precautions (5.1, 5.2), Drug Interactions (7.1), Use in Specific Populations (8.1, 8.2), Overdosage (10)]*.

5.4 Hypersensitivity Reactions

Serious or severe hypersensitivity reactions have been reported in association with other integrase inhibitors and could occur with APRETUDE *[see Adverse Reactions (6.1)]*. Administration of cabotegravir oral lead-in dosing was used in clinical studies to help identify participants who may be at risk of a hypersensitivity reaction. Remain vigilant and discontinue APRETUDE if a hypersensitivity reaction is suspected *[see Dosage and Administration (2.4), Contraindications (4), Adverse Reactions (6)]*.

Discontinue APRETUDE immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, mucosal involvement [oral blisters or lesions], conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver transaminases, should be monitored and appropriate therapy initiated. For information regarding the long-acting properties of APRETUDE *[see Warnings and Precautions (5.3)]*.

5.5 Hepatotoxicity

Hepatotoxicity has been reported in a limited number of individuals receiving cabotegravir with or without known pre-existing hepatic disease or identifiable risk factors *[see Adverse Reactions (6.1)]*.

Clinical and laboratory monitoring should be considered and APRETUDE should be

discontinued if hepatotoxicity is suspected and individuals managed as clinically indicated. For information regarding the long-acting properties of APRETUDE [see *Warnings and Precautions (5.3)*].

5.6 Depressive Disorders

Depressive disorders (including depression, depressed mood, major depression, persistent depressive disorder, suicide ideation or attempt) have been reported with APRETUDE [see *Adverse Reactions (6.1)*]. Promptly evaluate individuals with depressive symptoms to assess whether the symptoms are related to APRETUDE and to determine whether the risks of continued therapy outweigh the benefits.

5.7 Risk of Reduced Drug Concentration of APRETUDE Due to Drug Interactions

The concomitant use of APRETUDE and other drugs may result in reduced drug concentration of APRETUDE [see *Contraindications (4)*, *Drug Interactions (7.2, 7.3)*].

See Table 8 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during use of, and after discontinuation of APRETUDE; review concomitant medications during use of APRETUDE [see *Drug Interactions (7.3, 7.4)*].

6 ADVERSE REACTIONS

The following adverse reactions are described below and in other sections of the labeling:

- Hypersensitivity reactions [see *Warnings and Precautions (5.4)*]
- Hepatotoxicity [see *Warnings and Precautions (5.5)*]
- Depressive disorders [see *Warnings and Precautions (5.6)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect rates observed in practice.

Clinical Trials Experience in Adults

The safety assessment of APRETUDE is based on the analysis of data from 2 international, multicenter, double-blind trials, HPTN 083 and HPTN 084 [see *Clinical Studies (14.1)*].

Adverse reactions were reported while on blinded study product following exposure to APRETUDE extended-release injectable suspension and oral cabotegravir tablets as oral lead-in. The median time on blinded study product in HPTN 083 was 65 weeks and 2 days (range: 1 day to 156 weeks and 1 day), with a total exposure on cabotegravir of 3,231 person-years. The median time on blinded study product in HPTN 084 was 64 weeks and 1 day (range: 1 day to 153 weeks and 1 day), with a total exposure on cabotegravir of 2,009 person-years.

The most common adverse reactions regardless of severity reported in at least 1% of participants in HPTN 083 or HPTN 084 are presented in Table 4.

In HPTN 083, 6% of participants in the group receiving APRETUDE intramuscular injection every 2 months and 4% of participants receiving oral TRUVADA [emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF)] once daily discontinued due to adverse events (all causality). Non-injection-site-associated adverse events leading to discontinuation and occurring in $\geq 1\%$ of participants were increased alanine aminotransferase with APRETUDE and TRUVADA.

In HPTN 084, 1% of participants receiving APRETUDE and 1% of participants receiving TRUVADA discontinued due to adverse events. The most commonly reported adverse event (all causality) leading to discontinuation was increased alanine aminotransferase ($<1\%$) with APRETUDE and TRUVADA. The side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trials.

Table 4. Adverse Drug Reactions^a (All Grades) Reported in at Least 1% of Participants Receiving APRETUDE in Either HPTN 083 or HPTN 084

Adverse Reactions	HPTN 083		HPTN 084	
	APRETUDE Every 2 Months (n = 2,281)	TRUVADA Once Daily (n = 2,285)	APRETUDE Every 2 Months (n = 1,614)	TRUVADA Once Daily (n = 1,610)
Injection site reactions ^b	82%	35%	38%	11%
Diarrhea	4%	5%	4%	4%
Headache	4%	3%	12%	13%
Pyrexia ^c	4%	$<1\%$	$<1\%$	$<1\%$
Fatigue ^d	4%	2%	3%	3%
Sleep disorders ^e	3%	3%	1%	1%
Nausea	3%	5%	4%	8%
Dizziness	2%	3%	4%	6%
Flatulence	1%	1%	$<1\%$	$<1\%$
Abdominal pain ^f	1%	1%	2%	2%
Vomiting	$<1\%$	1%	2%	5%
Myalgia	$<1\%$	$<1\%$	2%	1%
Rash ^g	$<1\%$	$<1\%$	2%	1%
Decreased appetite	$<1\%$	$<1\%$	2%	4%
Somnolence	$<1\%$	$<1\%$	2%	2%
Back pain	$<1\%$	$<1\%$	1%	$<1\%$
Upper respiratory tract infection	0	$<1\%$	4%	4%

^a Adverse reactions defined as “treatment-related” as assessed by the investigator, with exception of injection site reactions, where all injection site reactions were reported regardless of causality.

^b Participants who received injection: HPTN 083, APRETUDE (n = 2,117) and TRUVADA (n = 2,081); HPTN 084, APRETUDE (n = 1,519) and TRUVADA (n = 1,516).

^c Pyrexia includes pyrexia, feeling hot, chills, influenza-like illness.

^d Fatigue includes fatigue, malaise.

^e Sleep disorders includes insomnia, abnormal dreams.

^f Abdominal pain includes abdominal pain, upper abdominal pain.

^g Rash includes rash, erythema, pruritis, macular, papular, maculopapular.

Injection-Associated Adverse Reactions

Local Injection Site Reactions (ISRs) with APRETUDE: The most frequent adverse reactions associated with the intramuscular administration of APRETUDE in HPTN 083 were ISRs. After 20,286 injections, 8,900 ISRs were reported. Of the 2,117 participants who received at least one injection of APRETUDE, 1,740 (82%) participants experienced at least one ISR, of which a total of 3% of participants discontinued APRETUDE because of ISRs. Among the participants who received APRETUDE and experienced at least one ISR, the maximum severity of reactions was mild (Grade 1) in 41% of participants, moderate (Grade 2) in 56% of participants, and severe (Grade 3) in 3% of participants. The median duration of overall ISR events was 4 days. The proportion of participants reporting ISRs at each visit and the severity of the ISRs decreased over time. The most commonly reported ISRs (all causality and grades) in at least 1% of participants who received APRETUDE and experienced at least one ISR from HPTN 083 are presented in Table 5.

The most frequent adverse reactions associated with the intramuscular administration of APRETUDE in HPTN 084 were ISRs. After 13,068 injections, 1,171 ISRs were reported. Of the 1,519 participants who received at least one injection of APRETUDE, 578 (38%) participants experienced at least one ISR. No participants discontinued APRETUDE because of ISRs. Among the participants who received APRETUDE and experienced at least one ISR, the maximum severity of reactions was mild (Grade 1) in 66% of participants, moderate (Grade 2) in 34% of participants, and severe (Grade 3) in less than 1% of participants. The median duration of overall ISR events was 8 days. The proportion of participants reporting ISRs at each visit and the severity of the ISRs generally decreased over time. The most commonly reported ISRs (all causality and grades) in at least 1% of participants who received APRETUDE and experienced at least one ISR from HPTN 084 are presented in Table 5.

Table 5. Injection Site Reactions (All Grades) Reported in at Least 1% of Participants who Experienced at Least One Injection Site Reaction (All Causality) with APRETUDE in Either HPTN 083 or HPTN 084

Injection Site Reactions	HPTN 083		HPTN 084	
	APRETUDE (n = 1,740)	TRUVADA ^a (n = 724)	APRETUDE (n = 578)	TRUVADA ^a (n = 166)
Pain/tenderness	98%	95%	90%	87%
Nodules	15%	2%	14%	2%
Induration	15%	<1%	12%	2%
Swelling	12%	1%	18%	3%
Bruising	4%	4%	1%	0
Erythema	4%	2%	5%	2%
Pruritus	3%	3%	6%	11%
Warmth	3%	1%	<1%	0
Anesthesia	1%	2%	1%	2%
Abscess	<1%	0	2%	3%

Discoloration	<1%	0	1%	0
---------------	-----	---	----	---

^a Placebo injectable suspension: intralipid 20% fat emulsion.

Other Injection-Associated Adverse Reactions: In the HPTN 083 clinical trial, an increased incidence of pyrexia (including pyrexia, feeling hot, chills, influenza-like illness) (4%) was reported by participants receiving APRETUDE compared with participants receiving TRUVADA (<1%). There were no differences reported in the incidence of pyrexia between groups in HPTN 084.

Vasovagal or pre-syncopal reactions considered treatment related were reported in <1% of participants after injection with APRETUDE in HPTN 083. None were reported as treatment related by the investigators in HPTN 084.

Less Common Adverse Reactions

The following select adverse reactions (regardless of severity) occurred in <1% of participants receiving APRETUDE in HPTN 083 or HPTN 084.

Hepatobiliary Disorders: Hepatotoxicity.

Investigations: Weight increase (see below).

Psychiatric Disorders: Depression.

Weight Increase

At the Week 41 and Week 97 timepoints in HPTN 083, participants who received APRETUDE gained a median of 1.2 kg (Interquartile Range [IQR]; -1.0, 3.5; n = 1,623) and 2.1 kg (IQR; -0.9, 5.9; n = 601) in weight from baseline. Those who received TRUVADA gained a median of 0 kg (IQR; -2.1, 2.4; n = 1,611) and 1 kg (IQR; -1.9, 4.0; n = 598) in weight from baseline, respectively.

At the Week 41 and 97 timepoints in HPTN 084, participants who received APRETUDE gained a median of 2 kg (IQR; 0.0, 5.0; n = 1,151) and 4 kg (IQR; 0.0, 8.0; n = 216) in weight from baseline, respectively. Those who received TRUVADA gained a median of 1 kg (IQR; -1.0, 4.0; n = 1,131) and 3 kg (IQR; -1.0, 6.0; n = 218) in weight from baseline, respectively.

Laboratory Abnormalities

Grade 3 or 4 post-baseline maximum toxicity laboratory abnormalities for HPTN 083 or HPTN 084 are summarized in Table 6.

Table 6. Laboratory Abnormalities (Grades 3 to 4) in ≥1% of Participants in Either HPTN 083 or HPTN 084

Laboratory Parameter	HPTN 083		HPTN 084	
	APRETUDE Every 2 Months (n = 2,281)	TRUVADA Once Daily (n = 2,285)	APRETUDE Every 2 Months (n = 1,614)	TRUVADA Once Daily (n = 1,610)
ALT (≥5.0 x ULN)	2%	2%	<1%	1%
AST (≥5.0 x ULN)	3%	3%	<1%	<1%
Creatine phosphokinase	150%	140%	20%	20%

($\geq 10.0 \times \text{ULN}$)	13 / 0	14 / 0	2 / 0	2 / 0
Lipase ($\geq 3.0 \times \text{ULN}$)	3%	3%	<1%	<1%
Creatinine ($>1.8 \times \text{ULN}$) or increase to $\geq 1.5 \times$ baseline)	3%	3%	5%	4%

ALT = Alanine transaminase, ULN = upper limit of normal, AST = Aspartate aminotransferase.

Serum Lipids: Changes from baseline to Month 15 in total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol to HDL ratio in HPTN 083 and HPTN 084 are presented in Table 7.

Table 7. Fasting Lipid Values, Median Change from Baseline^a at Week 57, Reported in HPTN 083 and HPTN 084

	HPTN 083		HPTN 084	
	APRETUDE	TRUVADA	APRETUDE	TRUVADA
Total cholesterol (mg/dL)	+1.0	-10.0	+0.2	-3.9
LDL cholesterol (mg/dL)	+1.0	-6.0	-1.1	-5.0
HDL cholesterol (mg/dL)	-0.2	-3.0	-0.8	-2.6
Triglycerides (mg/dL)	+2.7	0.0	+3.1	+0.7
Total cholesterol: HDL cholesterol ratio	+0.1	+0.0	+0.1	+0.1

^a Nearly 60% of participants with baseline data available had Week 57 data available in both arms of both trials. Within each trial, baseline values were comparable among participants receiving APRETUDE and TRUVADA.

Clinical Trials Experience in Adolescents

In adolescents receiving APRETUDE for HIV-1 PrEP, the safety data were comparable to the safety data reported in adults receiving APRETUDE for HIV-1 PrEP [see *Use in Specific Populations* (8.4)].

7 DRUG INTERACTIONS

7.1 Use of Other Antiretroviral Drugs after Discontinuation of APRETUDE

Residual concentrations of cabotegravir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer). These residual concentrations are not expected to affect the exposures of antiretroviral drugs that are initiated after discontinuation of APRETUDE [see *Warnings and Precautions* (5.3), *Drug Interactions* (7.4), *Clinical Pharmacology* (12.3)].

7.2 Potential for Other Drugs to Affect APRETUDE

Cabotegravir is primarily metabolized by UGT1A1 with some contribution from UGT1A9. Drugs that are strong inducers of UGT1A1 or 1A9 are expected to decrease cabotegravir plasma concentrations; therefore, coadministration of APRETUDE with these drugs is contraindicated [see *Contraindications* (4)].

7.3 Established and Other Potentially Significant Drug Interactions

Information regarding potential drug interactions with cabotegravir is provided in Table 8. These recommendations are based on either drug interaction trials following oral administration of cabotegravir or predicted interactions due to the expected magnitude of the interaction [see *Contraindications (4)*, *Warnings and Precautions (5.7)*, *Clinical Pharmacology (12.3)*]. Table 8 includes potentially significant interactions but is not all inclusive.

Table 8. Drug Interactions with APRETUDE

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓ Cabotegravir	Coadministration is contraindicated with APRETUDE due to potential for significant decreases in plasma concentration of APRETUDE.
Antimycobacterials: Rifampin Rifapentine	↓ Cabotegravir	
Antimycobacterial: Rifabutin	↓ Cabotegravir	When rifabutin is started before or concomitantly with the first initiation injection of APRETUDE, the recommended dosing of APRETUDE is one 600-mg (3-mL) injection, followed 2 weeks later by a second 600-mg (3-mL) initiation injection and monthly thereafter while on rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule of APRETUDE is 600 mg (3 mL) monthly while on rifabutin. After stopping rifabutin, the recommended dosing schedule of APRETUDE is 600 mg (3 mL) every 2 months.
Narcotic analgesic: Methadone	↔ Cabotegravir ↓ Methadone	No dose adjustment of methadone is required when starting coadministration of methadone with APRETUDE. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some individuals.

↑ = Increase, ↓ = Decrease, ↔ = No change.

7.4 Drugs without Clinically Significant Interactions with Cabotegravir

Based on drug interaction study results, the following drugs can be coadministered with

cabotegravir (non-antiretrovirals) or given after discontinuation of cabotegravir (antiretrovirals and non-antiretrovirals) without a dose adjustment: etravirine, midazolam, oral contraceptives containing levonorgestrel and ethinyl estradiol, and rilpivirine [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to APRETUDE during pregnancy. Healthcare providers are encouraged to register individuals by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

There are insufficient human data on the use of APRETUDE during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. While there are insufficient human data to assess the risk of neural tube defects (NTDs) with exposure to APRETUDE during pregnancy, NTDs were associated with dolutegravir, another integrase inhibitor. Healthcare providers should discuss the benefit-risk of using APRETUDE with individuals of childbearing potential or during pregnancy.

Cabotegravir use in pregnant women has not been evaluated. APRETUDE should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

The APR has been established to monitor for birth defects following prenatal exposure to antiretrovirals. The rate of miscarriage is not reported in the APR. The background rate for major birth defects in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) is 2.7%. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at <20 weeks' gestation.

In animal reproduction studies with oral cabotegravir, a delay in the onset of parturition and increased stillbirths and neonatal deaths were observed in a rat pre- and postnatal development study at >28 times the exposure at the recommended human dose (RHD). No evidence of adverse developmental outcomes was observed with oral cabotegravir in rats or rabbits (>28 times or similar to the exposure at the RHD, respectively) given during organogenesis (*see Data*).

Clinical Considerations

Cabotegravir is detected in systemic circulation for up to 12 months or longer after discontinuing injections of APRETUDE; therefore, consideration should be given to the potential for fetal exposure during pregnancy [see *Warnings and Precautions* (5.3)].

Data

Human Data: Data from a birth outcome surveillance study in Botswana showed that

dolutegravir, another integrase inhibitor, was associated with increased risk of NTDs when administered at the time of conception and in early pregnancy. Data from clinical trials are insufficient to address this risk with cabotegravir.

Animal Data: Cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from 15 days before cohabitation, during cohabitation, and from Gestation Days 0 to 17. There were no effects on fetal viability when fetuses were delivered by caesarean, although a minor decrease in fetal body weight was observed at 1,000 mg/kg/day (>28 times the exposure in humans at the RHD). No drug-related fetal toxicities were observed at 5 mg/kg/day (approximately 13 times the exposure in humans at the RHD), and no drug-related fetal malformations were observed at any dose.

Cabotegravir was administered orally to pregnant rabbits at 0, 30, 500, or 2,000 mg/kg/day from Gestation Days 7 to 19. No drug-related fetal toxicities were observed at 2,000 mg/kg/day (approximately 0.7 times the exposure in humans at the RHD).

In a rat pre- and postnatal development study, cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from Gestation Day 6 to Lactation Day 21. A delay in the onset of parturition and increases in the number of stillbirths and neonatal deaths by Lactation Day 4 were observed at 1,000 mg/kg/day (>28 times the exposure in humans at the RHD); there were no alterations to growth and development of surviving offspring. In a cross-fostering study, similar incidences of stillbirths and early postnatal deaths were observed when rat pups born to cabotegravir-treated mothers were nursed from birth by control mothers. There was no effect on neonatal survival of control pups nursed from birth by cabotegravir-treated mothers. A lower dose of 5 mg/kg/day (13 times the exposure at the RHD) was not associated with delayed parturition or neonatal mortality in rats. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in fetal tissue.

8.2 Lactation

Risk Summary

It is not known if cabotegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, cabotegravir was present in milk (*see Data*). If cabotegravir is present in human milk, residual exposures may remain for 12 months or longer after the last injections have been administered [*see Warnings and Precautions (5.3)*].

Because of detectable cabotegravir concentrations in systemic circulation for up to 12 months or longer after discontinuing injections of APRETUDE, it is recommended that women breastfeed only if the expected benefit justifies the potential risk to the infant.

Data

Animal Data: Animal lactation studies with cabotegravir have not been conducted. However, cabotegravir was detected in the plasma of nursing pups on Lactation Day 10 in the rat pre- and postnatal development study.

8.4 Pediatric Use

The safety and effectiveness of APRETUDE for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from 2 adequate and well-controlled trials

of APRETUDE for HIV-1 PrEP in adults with additional safety and pharmacokinetic data from studies in HIV-1 infected adults who were administered CABENUVA, and in HIV-1 infected pediatric subjects who were administered separate components of CABENUVA in addition to their current antiretroviral therapy [see *Dosage and Administration* (2.5), *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), *Clinical Studies* (14.2)].

APRETUDE for HIV-1 PrEP is being evaluated in 2 open-label multicenter clinical trials in adolescent individuals. Fifty-nine adolescents have been enrolled. Of these, 54 adolescent participants received one or more injections. In adolescents receiving APRETUDE for HIV-1 PrEP, the safety data were comparable to the safety data reported in adults receiving APRETUDE for HIV-1 PrEP.

While using APRETUDE, HIV-1 testing should be conducted prior to initiating APRETUDE (with or without an oral lead-in with oral cabotegravir) and prior to each injection of APRETUDE. Adolescents may benefit from more frequent visits and counseling to support adherence to the dosing and testing schedule [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1)].

The safety, efficacy, and pharmacokinetics of APRETUDE in pediatric participants younger than 12 years of age or weighing <35 kg have not been established.

8.5 Geriatric Use

No dose adjustment is required in elderly individuals. There are limited data available on the use of APRETUDE in individuals aged 65 years and older. In general, caution should be exercised in administration of APRETUDE in elderly individuals reflecting greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

Based on studies with oral cabotegravir, no dosage adjustment of APRETUDE is necessary for individuals with mild (creatinine clearance ≥ 60 to < 90 mL/min) or moderate renal impairment (creatinine clearance ≥ 30 to < 60 mL/min). In individuals with severe renal impairment (creatinine clearance 15 to < 30 mL/min) or end-stage renal disease (creatinine clearance < 15 mL/min), increased monitoring for adverse effects is recommended [see *Clinical Pharmacology* (12.3)]. In individuals with end-stage renal disease not on dialysis, effects on the pharmacokinetics of cabotegravir are unknown. As cabotegravir is >99% protein bound, dialysis is not expected to alter exposures of cabotegravir.

8.7 Hepatic Impairment

Based on studies with oral cabotegravir, no dosage adjustment of APRETUDE is necessary for individuals with mild or moderate hepatic impairment (Child-Pugh A or B). The effect of severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of cabotegravir is unknown [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

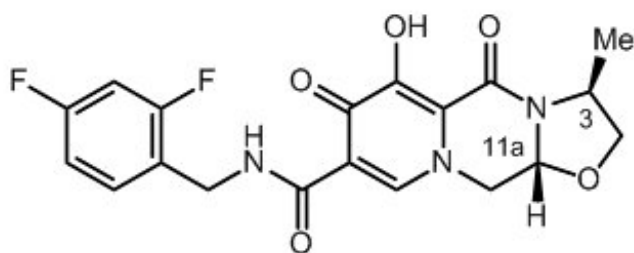
There is no known specific treatment for overdose with APRETUDE. If overdose occurs, monitor the individual and apply standard supportive treatment as required as well as

observation of the clinical status of the individual. As APRETUDE is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis. Consider the prolonged exposure to APRETUDE following an injection when assessing treatment needs and recovery [see *Warnings and Precautions* (5.5)].

11 DESCRIPTION

APRETUDE contains cabotegravir extended-release injectable suspension, an HIV INSTI.

The chemical name of cabotegravir is (3*S*,11*aR*)-N-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide. The empirical formula is C₁₉H₁₇F₂N₃O₅ and the molecular weight is 405.35 g/mol. It has the following structural formula:



Cabotegravir extended-release injectable suspension is a white to light pink free-flowing suspension for intramuscular injection in a sterile single-dose vial. Each vial delivers 600 mg/3 mL (200 mg/mL) of cabotegravir and mannitol (105 mg), polyethylene glycol (PEG) 3350 (60 mg), polysorbate 20 (60 mg), and Water for Injection.

The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cabotegravir is an HIV-1 antiretroviral drug [see *Microbiology* (12.4)] in a long-acting formulation.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose of cabotegravir 150 mg orally every 12 hours (10 times the recommended total daily oral lead-in dosage of APRETUDE), the QT interval is not prolonged to any clinically relevant extent. Administration of 3 doses of cabotegravir 150 mg orally every 12 hours resulted in a geometric mean C_{max} approximately 2.8-fold and 5.6-fold above the geometric mean steady-state C_{max} associated with the recommended 30-mg dose of oral cabotegravir and the recommended 600-mg dose given every 2 months of cabotegravir extended-release injectable suspension, respectively.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic properties of cabotegravir are provided in Table 9. The multiple-dose pharmacokinetic parameters are provided in Table 10. For the pharmacokinetic properties of oral cabotegravir, refer to the full prescribing information for oral cabotegravir.

Table 9. Pharmacokinetic Properties of Cabotegravir

	Cabotegravir
Absorption^a	
T _{max} (days), median	7
Distribution	
% Bound to human plasma proteins	>99.8
Blood-to-plasma ratio	0.52
CSF-to-plasma concentration ratio (median [range]) ^b	0.003 (0.002 to 0.004)
Elimination	
t _{1/2} (weeks) mean ^c	5.6 to 11.5
Metabolism	
Metabolic pathways	UGT1A1 UGT1A9 (minor)
Excretion	
Major route of elimination	Metabolism
% of dose excreted as total ¹⁴ C (unchanged drug) in urine ^d	27 (0)
% of dose excreted as total ¹⁴ C (unchanged drug) in feces ^d	59 (47)

CSF = Cerebrospinal fluid.

^a When taken orally with a high-fat meal versus fasted, the AUC_(0-inf) (geometric mean ratio [90% CI] of cabotegravir are 1.14 [1.02, 1.28]).

^b The clinical relevance of CSF-to-plasma concentration ratios is unknown. Concentrations were measured at steady-state 1 week after intramuscular administration of cabotegravir extended-release injectable suspensions given monthly or every 2 months.

^c Elimination half-life driven by slow absorption rate from the intramuscular injection site.

^d Dosing in mass balance studies: single-dose oral administration of [¹⁴C] cabotegravir.

Table 10. Pharmacokinetic Parameters following Once-Daily Oral Cabotegravir and following Initiation and Every-2-Month Continuation Intramuscular Injections of APRETUDE

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)^a		
		AUC_(0-tau)^b (mcg•h/mL)	C_{max} (mcg/mL)	C_{tau} (mcg/mL)
Oral lead-in ^c	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
Initial injection ^d	600 mg IM	1,591	8.0	1.5

	initial dose	(714; 3,245)	(5.3, 11.9)	(0.65, 2.9)
Every-2-month injection ^e	600 mg IM every 2 months	3,764 (2,431; 5,857)	4.0 (2.3, 6.8)	1.6 (0.8, 3.0)

Specific Populations

No clinically significant differences in the pharmacokinetics of cabotegravir were observed based on age, sex, race/ethnicity, BMI, or UGT1A1 polymorphisms. There are no data available for the use of cabotegravir in participants with hepatitis B virus and hepatitis C virus co-infection in PrEP studies.

Renal Impairment: With oral cabotegravir, no clinically significant differences in the pharmacokinetics of cabotegravir are expected in individuals with mild, moderate, or severe renal impairment. Cabotegravir has not been studied in participants with end-stage renal disease not on dialysis. As cabotegravir is >99% protein bound, dialysis is not expected to alter exposures of cabotegravir [see *Use in Specific Populations (8.6)*].

Hepatic Impairment: No clinically significant differences in the pharmacokinetics of cabotegravir are expected in mild to moderate (Child-Pugh A or B) hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of cabotegravir has not been studied [see *Use in Specific Populations (8.7)*].

Gender: Population pharmacokinetic analyses revealed no clinically relevant effect of gender on the exposure of cabotegravir. In addition, no clinically relevant differences in plasma cabotegravir concentrations were observed in PrEP studies by gender, including in cisgender men and transgender women (+/- hormone use). Therefore, no dose adjustment is necessary based on gender.

Geriatrics: No dose adjustment is required in elderly individuals. There are limited data available on the use of cabotegravir in individuals aged 65 years and older. In general, caution should be exercised in administration of APRETUDE in elderly individuals reflecting greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy [see *Use in Specific Populations (8.5)*].

Pediatrics: Population pharmacokinetic analyses revealed no clinically relevant differences in exposure between the HIV-1 infected adolescent and HIV-1 infected and uninfected adult participants from the cabotegravir development program; therefore, no dosage adjustment is needed for adolescents weighing at least 35 kg (Table 11).

Table 11. Predicted Pharmacokinetic Parameters^a following Once-Daily Oral Cabotegravir and following Initiation and Every-2-Month Continuation Intramuscular Injections of APRETUDE in Adolescent Participants Aged 12 to Younger than 18 Years (≥35 kg)

Dosing Phase	Dosage Regimen	Geometric Mean (5 th , 95 th Percentile) ^a		
		AUC _(0-tau) ^b (mcg•h/mL)	C _{max} (mcg/mL)	C _{tau} (mcg/mL)
Oral lead-in ^c	30 mg once daily	193 (106, 346)	14.4 (8.02, 25.5)	5.79 (2.48, 12.6)
Initial injection ^d	600 mg IM initial dose	2,123 (881; 4,938)	11.2 (5.63, 21.5)	1.84 (0.64, 4.52)
Every-2-month	600 mg IM	4,871	7.23	2.01

injection ^e	every 2-months	(2,827; 8,232)	(3.76, 14.1)	(0.64, 4.73)
------------------------	----------------	----------------	--------------	--------------

IM = intramuscular.

^a Pharmacokinetic (PK) parameter values were based on population PK model simulations in a virtual HIV-1 infected adolescent population weighing 35 to 156 kg.

^b tau is dosing interval: 24 hours for oral administration, 1 month for the initial injection, and 2 months for every 2 months for IM injections of extended-release injectable suspension.

^c Oral lead-in pharmacokinetic parameter values represent steady state.

^d Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the AUC_(0-tau) and C_{tau} values reflect the initial injection.

^e PK parameter values represent steady state.

Drug Interaction Studies

Cabotegravir is not a clinically relevant inhibitor of the following enzymes and transporters: cytochrome P450 (CYP)1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4; UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17; P-glycoprotein (P-gp); breast cancer resistance protein (BCRP); bile salt export pump (BSEP); organic cation transporter (OCT)1, OCT2; organic anion transporter polypeptide (OATP)1B1, OATP1B3; multidrug and toxin extrusion transporter (MATE) 1, MATE 2-K; and multidrug resistance protein (MRP)2 or MRP4.

In vitro, cabotegravir inhibited renal OAT1 (IC₅₀ = 0.81 microM) and OAT3 (IC₅₀ = 0.41 microM). Based on physiologically based pharmacokinetic (PBPK) modeling, cabotegravir may increase the AUC of OAT1/3 substrates up to approximately 80%.

In vitro, cabotegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

Simulations using PBPK modeling show that no clinically significant interaction is expected during coadministration of cabotegravir with drugs that inhibit UGT1A1.

In vitro, cabotegravir was not a substrate of OATP1B1, OATP1B3, OATP2B1, or OCT1.

Cabotegravir is a substrate of P-gp and BCRP in vitro; however, because of its high permeability, no alteration in cabotegravir absorption is expected with coadministration of P-gp or BCRP inhibitors.

Drug interaction studies were not conducted with injectable cabotegravir. Drug interaction studies with oral cabotegravir are summarized in Tables 12 and 13.

Table 12. Effect of Coadministered Drugs on the Pharmacokinetics of Cabotegravir

Coadministered Drug(s) and Dose(s)	Dose of Cabotegravir	n	Geometric Mean Ratio (90% CI) of Cabotegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C _{max}	AUC	C _{tau} or C ₂₄

Etravirine 200 mg twice daily	30 mg once daily	12	1.04 (0.99, 1.09)	1.01 (0.96, 1.06)	1.00 (0.94, 1.06)
Rifabutin 300 mg once daily	30 mg once daily	12	0.83 (0.76, 0.90)	0.77 (0.74, 0.83)	0.74 (0.70, 0.78)
Rifampin 600 mg once daily	30-mg single dose	15	0.94 (0.87, 1.02)	0.41 (0.36, 0.46)	0.50 (0.44, 0.57)
Rilpivirine 25 mg once daily	30 mg once daily	11	1.05 (0.96, 1.15)	1.12 (1.05, 1.19)	1.14 (1.04, 1.24)

n = Maximum number of participants with data, CI = Confidence Interval.

Table 13. Effect of Cabotegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Cabotegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Cabotegravir No Effect = 1.00		
			C _{max}	AUC	C _{tau} or C ₂₄
Ethinyl estradiol 0.03 mg once daily	30 mg once daily	19	0.92 (0.83, 1.03)	1.02 (0.97, 1.08)	1.00 (0.92, 1.10)
Levonorgestrel 0.15 mg once daily	30 mg once daily	19	1.05 (0.96, 1.15)	1.12 (1.07, 1.18)	1.07 (1.01, 1.15)
Midazolam 3 mg	30 mg once daily	12	1.09 (0.94, 1.26)	1.10 (0.95, 1.26)	NA
Rilpivirine 25 mg once daily	30 mg once daily	11	0.96 (0.85, 1.09)	0.99 (0.89, 1.09)	0.92 (0.79, 1.07)

n = Maximum number of participants with data, CI = Confidence Interval; NA = Not available.

12.4 Microbiology

Mechanism of Action

Cabotegravir inhibits HIV integrase by binding to the integrase active site and blocking

the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration that is essential for the HIV replication cycle. The mean 50% inhibitory concentration (IC₅₀) value of cabotegravir in a strand transfer assay using purified recombinant HIV-1 integrase was 3.0 nM.

Antiviral Activity in Cell Culture

Cabotegravir exhibited antiviral activity against laboratory strains of HIV-1 (subtype B, n = 4) with mean 50 percent effective concentration (EC₅₀) value of 0.22 nM to 1.7 nM in peripheral blood mononuclear cells (PBMCs) and 293 cells. Cabotegravir demonstrated antiviral activity in PBMCs against a panel of 24 HIV-1 clinical isolates (3 in each of group M subtypes A, B, C, D, E, F, and G and 3 in group O) with a median EC₅₀ value of 0.19 nM (range: 0.02 nM to 1.06 nM, n = 24). The median EC₅₀ value against subtype B clinical isolates was 0.05 nM (range: 0.02 to 0.50 nM, n = 3). Against clinical HIV-2 isolates, the median EC₅₀ value was 0.12 nM (range: 0.10 nM to 0.14 nM, n = 4).

In cell culture, cabotegravir was not antagonistic in combination with the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine, or the nucleoside reverse transcriptase inhibitors (NRTIs) FTC, lamivudine (3TC), or TDF.

Resistance

Cell Culture: Cabotegravir-resistant viruses were selected during passage of HIV-1 strain IIB in MT-2 cells in the presence of cabotegravir. Amino acid substitutions in integrase that emerged and conferred decreased susceptibility to cabotegravir included Q146L (fold change: 1.3 to 4.6), S153Y (fold change: 2.8 to 8.4), and I162M (fold change: 2.8). The integrase substitution T124A also emerged alone (fold change: 1.1 to 7.4 in cabotegravir susceptibility), in combination with S153Y (fold change: 3.6 to 6.6 in cabotegravir susceptibility) or I162M (2.8-fold change in cabotegravir susceptibility). Cell culture passage of virus harboring integrase substitutions Q148H, Q148K, or Q148R selected for additional substitutions (C56S, V72I, L74M, V75A, T122N, E138K, G140S, G149A, and M154I), with substituted viruses having reduced susceptibility to cabotegravir of 2.0-fold to 410-fold change. The combinations of E138K+Q148K and V72I+E138K+Q148K conferred the greatest reductions of 53-fold to 260-fold change and 410-fold change, respectively.

Clinical Trials: There were 12 incident infections and 4 prevalent infections among subjects in the APREUDE arm of HPTN 083. Genotypic data were generated for viruses from 13 of these 16 subjects (4 subjects with prevalent infections and 9 subjects with incident infections) and phenotypic data were generated for 3 of these viruses. INSTI resistance-associated substitutions were detected in 5 viruses from subjects who achieved target plasma concentrations of cabotegravir (≥ 0.65 mcg/mL [1.6 μ M]) and included R263K (2-fold less susceptible to cabotegravir), E138A+Q148R (6-fold less susceptible to cabotegravir), E138K+Q148K, G140A+Q148R (13-fold less susceptible to cabotegravir), and L74I+E138E/K+G140G/S+Q148R+E157Q.

There were 3 incident infections and 1 prevalent infection among subjects in the APREUDE arm of HPTN 084. All 3 incident infections occurred during periods with cabotegravir exposures below the target concentration. No variants expressing INSTI resistance-associated substitutions were detected.

Cross-Resistance

Cross-resistance has been observed among INSTIs. Cabotegravir had reduced

susceptibility (>5-fold change) to recombinant HIV-1 strain NL432 viruses harboring the following integrase amino acid substitutions: G118R, Q148K, Q148R, T66K+L74M, E92Q+N155H, E138A+Q148R, E138K+Q148K/R, G140C+Q148R, G140S+Q148H/K/R, Y143H+N155H, and Q148R+N155H (range: 5.1-fold to 81-fold). The substitutions E138K+Q148K and Q148R+N155H conferred the greatest reductions in susceptibility of 81-fold and 61-fold, respectively.

Viruses harboring E138A+Q148R or G140A+Q148R with reduced susceptibility to cabotegravir were isolated from subjects using APREUDE in HPTN 083. These viruses remained susceptible to bictegravir and dolutegravir but had cross-resistance to elvitegravir and raltegravir.

Virologic failure isolates from cabotegravir+rilpivirine treatment in FLAIR, ATLAS, and ATLAS-2M exhibited cross-resistance to INSTIs and NNRTIs. All confirmed virologic isolates with genotypic evidence of cabotegravir resistance had cross-resistance to elvitegravir and raltegravir but retained phenotypic susceptibility to bictegravir and dolutegravir when tested.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies in mice and rats were conducted with cabotegravir. In mice, no drug-related increases in tumor incidence were observed at cabotegravir exposures (AUC) up to approximately 8 times (males) and 7 times (females) higher than those in humans at the RHD. In rats, no drug-related increases in tumor incidence were observed at cabotegravir exposures up to approximately 26 times higher than those in humans at the RHD.

Mutagenesis

Cabotegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Impairment of Fertility

In rats, no effects on fertility were observed at cabotegravir exposures (AUC) >20 times (male) and 28 times (female) the exposure in humans at the RHD.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adults for HIV-1 Pre-Exposure Prophylaxis

The safety and efficacy of APREUDE to reduce the risk of acquiring HIV-1 infection were evaluated in 2 randomized, double-blind, controlled, multinational trials, HPTN 083 in HIV-1 uninfected men and transgender women who have sex with men and have evidence of high-risk behavior for HIV-1 infection and HPTN 084 in HIV-1 uninfected cisgender women at risk of acquiring HIV-1.

Participants randomized to receive APREUDE initiated oral lead-in dosing with 1 oral cabotegravir 30-mg tablet and a placebo daily for up to 5 weeks, followed by APREUDE

600-mg (3-mL) intramuscular injection at months 1 and 2 and every 2 months thereafter and a daily placebo tablet. Participants randomized to receive TRUVADA initiated oral TRUVADA (TDF 300 mg/FTC 200 mg) and placebo daily for up to 5 weeks, followed by oral TRUVADA daily and placebo intramuscular injection at months 1 and 2 and every 2 months thereafter.

Trial 201738 (HPTN 083 [NCT02720094])

In HPTN 083, a non-inferiority study, 4,566 cisgender men and transgender women who have sex with men were randomized 1:1 and received either APRETUDE (n = 2,281) or TRUVADA (n = 2,285) as blinded study medication up to Week 153.

At baseline, the median age of participants was 26 years, 12% were transgender women, 72% were non-White, and 67% were younger than 30 years.

The primary endpoint was the rate of incident HIV-1 infections among participants randomized to daily oral cabotegravir and intramuscular injections of APRETUDE every 2 months compared with daily oral TRUVADA (corrected for early stopping). The primary analysis demonstrated the superiority of APRETUDE compared with TRUVADA with a 66% reduction in the risk of acquiring HIV-1 infection, hazard ratio (95% CI) 0.34 (0.18, 0.62); further testing revealed 1 of the infections on APRETUDE to be prevalent then yielding a 69% reduction in the risk of HIV-1 incident infection relative to TRUVADA (Table 14).

Table 14. HIV-1 Infection Results During Randomized Phase in HPTN 083: Extended Retrospective Virologic Testing with Readjudicated Endpoints^a

	APRETUDE (N = 2,278)	TRUVADA (N = 2,281)	Superiority <i>P</i> Value
Person-years	3,211	3,193	
HIV-1 infections (incidence rate per 100 person-years)	12 ^b (0.37)	39 (1.22)	
Hazard ratio (95% CI)	0.31 (0.16, 0.58)		0.0003

^a mITT from Supplemental Virology Report.

^b Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV-1 infections. As a result, 1 of the 13 HIV-1 incident infections in participants receiving APRETUDE was determined to be a prevalent infection. The original hazard ratio (95% CI) from the primary analysis is 0.34 (0.18, 0.62).

Figure 1. Cumulative Incidence of HIV-1 Infections in HPTN 083

Results from all subgroup analyses were consistent with the overall protective effect. A lower rate of incident HIV-1 infections was observed for participants randomized to APRETUDE compared with participants randomized to TRUVADA (Table 15).

Table 15. Incident of HIV-1 Infections by Subgroup in HPTN 083: Extended Retrospective Virologic Testing with Readjudicated Endpoints^a

Subgroup	APRETUDE Incidence per 100 Person- Years	APRETUDE Person-Years	TRUVADA Incidence per 100 Person- Years	TRUVADA Person- Years	Hazard Ratio (95% CI)
Age					
<30 years	0.47	2,110	1.66	1,987	0.29 (0.15, 0.59)
≥30 years	0.18	1,101	0.50	1,206	0.39 (0.08, 1.84)
Gender					
MSM ^b	0.35	2,836	1.14	2,803	0.32

					(0.16, 0.64)
TGW ^c	0.54	371	1.80	389	0.34 (0.08, 1.56)
Race (US)					
Black	0.58	691	2.28	703	0.26 (0.09, 0.76)
Non-Black	0.00	836	0.50	801	0.11 (0.00, 2.80)
Region					
US	0.26	1,528	1.33	1,504	0.21 (0.07, 0.60)
Latin America	0.49	1,020	1.09	1,011	0.47 (0.17, 1.35)
Asia	0.35	570	1.03	581	0.39 (0.08, 1.82)
Africa	1.08	93	2.07	97	0.63 (0.06, 6.50)

^a mITT from Supplemental Virology Report.

^b Cisgender men who have sex with men.

^c Transgender women who have sex with men.

Trial 201739 (HPTN 084 [NCT03164564])

In HPTN 084, a superiority study, 3,224 cisgender women were randomized 1:1 and received either APRETUDE (n = 1,614) or TRUVADA (n = 1,610) as blinded study medication up to Week 153.

At baseline, the median age of participants was 25 years, >99% were non-White, >99% were cisgender women, and 49% were <25 years of age.

The primary endpoint was the rate of incident HIV-1 infections among participants randomized to oral cabotegravir and injections of APRETUDE compared with oral TRUVADA (corrected for early stopping). The primary analysis demonstrated the superiority of APRETUDE compared with TRUVADA with an 88% reduction in the risk of acquiring incident HIV-1 infection, hazard ratio (95% CI) 0.12 (0.05, 0.31); further testing revealed 1 of the infections on APRETUDE to be prevalent then yielding a 90% reduction in the risk of HIV-1 incident infection relative to TRUVADA ([Table 16](#)).

Table 16. HIV-1 Infection Results during Randomized Phase in HPTN 084: Extended Retrospective Virologic Testing with Readjudicated Endpoints^a

	APRETUDE	TRUVADA	Superiority
--	-----------------	----------------	--------------------

	(N = 1,613)	(N = 1,610)	P Value
Person-years	1,960	1,946	
HIV-1 incident infections (incidence rate per 100 person-years)	3 ^b (0.15)	36 (1.85)	
Hazard ratio (95% CI)	0.10 (0.04, 0.27)		<0.0001

^a mITT from Supplemental Virology Report.

^b Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV-1 infections. As a result, 1 of the 4 HIV-1 incident infections in participants receiving APRETUDE was determined to be a prevalent infection. The original hazard ratio (95% CI) from the primary analysis is 0.12 (0.05, 0.31).

Figure 2. Cumulative Incidence of HIV-1 Infections in HPTN 084

Results from pre-planned subgroup analyses were consistent with the overall protective effect. A lower rate of incident HIV-1 infections was observed for participants randomized to APRETUDE compared with participants randomized to TRUVADA (Table 17).

Table 17. Incident of HIV-1 Infections by Subgroup in HPTN 084: Extended Retrospective Virologic Testing with Readjudicated Endpoints^a

	APRETUDE Incidence		TRUVADA Incidence		
--	-------------------------------	--	------------------------------	--	--

Subgroup	per 100 Person-Years	APRETUDE Person-Years	per 100 Person-Years	TRUVADA Person-Years	Hazard Ratio (95% CI)
Age					
<25 years	0.23	868	2.34	853	0.12 (0.03, 0.46)
≥25 years	0.09	1,093	1.46	1,093	0.09 (0.02, 0.49)
Body Mass Index					
<30	0.22	1,385	1.88	1,435	0.12 (0.04, 0.38)
≥30	0.00	575	1.76	511	0.04 (0.00, 0.93)

^a mITT from Supplemental Virology Report.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

APRETUDE is supplied in a kit containing one 600-mg/3-mL single-dose (200-mg/mL) vial of cabotegravir extended-release injectable suspension, 1 syringe, 1 vial adapter, and 1 needle for intramuscular injection (23 gauge, 1½ inch) (NDC 49702-264-23). The vial stopper is not made with natural rubber latex.

Storage and Handling

Store APRETUDE at 2°C to 25°C (36°F to 77°F) in the original carton until ready to use. Exposure up to 30°C permitted. Do not freeze. Do not mix with any other product or diluent.

If the pack has been stored in the refrigerator, the vial should be brought to room temperature prior to administration (not to exceed 30°C [86°F]).

Once the suspension has been drawn into the syringe, the injection should be administered as soon as possible, but may remain in the syringe for up to 2 hours. The filled syringes should not be placed in the refrigerator. If the medicine remains in the syringe for more than 2 hours, the filled syringe and needle must be discarded [see *Dosage and Administration* (2.7)].

17 PATIENT COUNSELING INFORMATION

Advise the individual to read the FDA-approved patient labeling (Patient Information).

Important Information for Uninfected Individuals Taking APRETUDE for HIV-1 PrEP

Advise HIV-1 uninfected individuals about the following [see *Warnings and Precautions* (5.1)]:

- APRETUDE should be used for PrEP as part of an overall HIV-1 infection prevention strategy, including adherence to the administration schedule and safer sex practices, including condoms, to reduce the risk of STIs.

- APRETUDE is not always effective in preventing HIV-1 acquisition [*see Clinical Studies (14.1)*]. The time from initiation of APRETUDE for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.
- Counsel individuals on the use of other prevention measures (e.g., knowledge of partner HIV-1 status, testing for STIs condom use). Inform individuals about and support their efforts in reducing sexual risk behavior.
- APRETUDE should be used to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-1 negative. HIV-1 resistance substitutions may emerge in individuals with undiagnosed HIV-1 infection who are taking only APRETUDE, because APRETUDE alone does not constitute a complete regimen for HIV-1 treatment; therefore, care should be taken to minimize the risk of initiating or continuing APRETUDE before confirming the individual is HIV-1 negative.
- If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute or primary HIV-1 infection.
- When using APRETUDE for HIV-1 PrEP, HIV-1 testing should be repeated prior to each injection of APRETUDE, and upon diagnosis of any other STIs.
- If an HIV-1 test indicates possible HIV-1 infection, or if symptoms consistent with acute HIV-1 infection develop following an exposure event, additional HIV testing to determine HIV status is needed. If an individual has confirmed HIV-1 infection, then the individual must be transitioned to a complete HIV-1 treatment regimen.
- Some individuals, such as adolescents, may benefit from frequent visits and counseling to support adherence.

Potential Risk of Resistance with APRETUDE

Advise individuals there is a potential risk of developing resistance to APRETUDE if HIV-1 is acquired either before or while taking APRETUDE or following discontinuation of APRETUDE [*see Warnings and Precautions (5.2)*].

To minimize this, it is essential that individuals are clinically reassessed for risk of HIV-1 acquisition and tested frequently to confirm HIV-1 negative status. Advise individuals who are confirmed to have with HIV-1 infection to consult with their healthcare professional, as HIV-1 treatment must be initiated [*see Warnings and Precautions (5.2)*].

Inform individuals that alternative forms of PrEP should be considered following discontinuation of APRETUDE for those at continuing risk of HIV-1 acquisition and initiated within 2 months of the final injection of APRETUDE [*see Warnings and Precautions (5.2)*].

Long-Acting Properties of APRETUDE

Advise individuals that APRETUDE is an extended-release injectable that may be systemically present for 12 months or longer and consideration should be taken regarding the prolonged release characteristics when APRETUDE is discontinued [*see Warnings and Precautions (5.3), Drug Interactions (7)*].

Adherence to APRETUDE

Counsel individuals about the importance of continued medication adherence and scheduled visits to help reduce the risk of acquiring HIV-1 infection and development of resistance [*see Dosage and Administration (2.3), Warnings and Precautions (5.1)*].

Hypersensitivity Reactions

Advise individuals to immediately contact their healthcare provider if they develop a rash. Instruct individuals to immediately stop taking APRETUDE and seek medical attention if they develop a rash associated with any of the following symptoms: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue, or mouth; difficulty breathing; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes; dark or tea-colored urine; pale-colored stools or bowel movements; nausea; vomiting; loss of appetite; or pain, aching, or sensitivity on the right side below the ribs). Advise individuals that if hypersensitivity occurs, they will be closely monitored, laboratory tests will be ordered, and appropriate therapy will be initiated [see *Warnings and Precautions* (5.4)].

Hepatotoxicity

Inform individuals that hepatotoxicity has been reported with cabotegravir [see *Warnings and Precautions* (5.5), *Adverse Reactions* (6.1)]. Inform individuals that clinical and laboratory monitoring should be considered and APRETUDE should be discontinued if hepatotoxicity is confirmed [see *Warnings and Precautions* (5.5)].

Depressive Disorders

Inform individuals that depressive disorders (including depression, depressed mood, major depression, persistent depressive disorder, suicide ideation or attempt) have been reported with APRETUDE [see *Adverse Reactions* (6.1)]. Advise individuals to seek prompt medical evaluation if they experience depressive symptoms [see *Warnings and Precautions* (5.6)].

Drug Interactions

Inform individuals that APRETUDE may interact with other drugs and may reduce exposure of APRETUDE; therefore, advise individuals to report to their healthcare provider the use of any other prescription or nonprescription medication [see *Contraindications* (4), *Warnings and Precautions* (5.7), *Drug Interactions* (7.2, 7.3)].

Missed Dose

Inform individuals that APRETUDE can remain in the body for up to 12 months or longer after receiving their last injection. Advise individuals that they should contact their healthcare provider if they miss or plan to miss a scheduled monthly injection visit and that oral dosing may be used to replace up to 2 consecutive monthly injections. Advise individuals that if they discontinue use of APRETUDE, they will need to take other medicines for HIV-1 PrEP [see *Dosage and Administration* (2.3, 2.6)].

Pregnancy Registry

Inform individuals that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to APRETUDE during pregnancy. Individuals who are of reproductive potential should be informed of the long duration of exposure of APRETUDE and that there is very limited clinical experience in human pregnancy [see *Warnings and Precautions* (5.3), *Use in Specific Populations* (8.1)].

Lactation

Inform individuals that due to the potential for adverse reactions and residual concentrations in the systemic circulation for up to 12 months or longer after discontinuing injections of APRETUDE, it is recommended that women breastfeed only if

the expected benefit justifies the potential risk to the infant.

APRETUDE and CABENUVA are trademarks owned by or licensed to the ViiV Healthcare companies.

The other brand listed is a trademark owned by or licensed to its respective owner and is not a trademark owned by or licensed to the ViiV Healthcare group of companies. The maker of this brand is not affiliated with and does not endorse the ViiV Healthcare group of companies or its products.

Manufactured for:

ViiV Healthcare

Research Triangle Park, NC 27709

by:

GlaxoSmithKline

Research Triangle Park, NC 27709

©2021 ViiV Healthcare group of companies or its licensor.

APR:1PI

Patient Information
APRETUDE (AP-reh-tood)
(cabotegravir extended-release injectable suspension)
for intramuscular use

What is the most important information I should know about APRETUDE?
Important information for people who receive APRETUDE to help reduce their risk of getting human immunodeficiency virus-1 (HIV-1) infection, also called pre-exposure prophylaxis or “PrEP”:

Before receiving APRETUDE to reduce your risk of getting HIV-1:

- **You must be HIV-1 negative to start APRETUDE. You must get tested to make sure that you do not already have HIV-1 infection.**
- **Do not receive APRETUDE for HIV-1 PrEP unless you are confirmed to be HIV-1 negative.**
- Some HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting APRETUDE or at any time while receiving APRETUDE. Symptoms of new HIV-1 infection include:

- | | |
|---|------------------------|
| o tiredness | o fever |
| o joint or muscle aches | o headache |
| o sore throat | o vomiting or diarrhea |
| o rash | o night sweats |
| o enlarged lymph nodes in the neck or groin | |

While you are receiving APRETUDE for HIV-1 PrEP:

- **APRETUDE does not prevent other sexually transmitted infections. Practice safer sex by using a latex or polyurethane condom to reduce the risk of getting sexually transmitted infections.**
- **You must stay HIV-1 negative to keep receiving APRETUDE for HIV-1 PrEP.**
 - o Know your HIV-1 status and the HIV-1 status of your partners.
 - o Ask your partners with HIV-1 if they are taking anti-HIV-1 medicines and have an undetectable viral load. An undetectable viral load is when the amount of virus in the blood is too low to be measured in a lab test. To maintain an undetectable viral load, your partners must keep taking HIV-1 medicine as prescribed. Your risk of getting HIV-1 is lower if your partners with HIV-1 are taking effective treatment.
 - o Get tested for HIV-1 with each APRETUDE injection or when your healthcare provider tells you. You should not miss any HIV-1 tests. If you become HIV-1 infected and continue receiving APRETUDE because you do not know you are HIV-1 infected, the HIV-1 infection may become harder to treat.
 - o Get tested for other sexually transmitted infections such as syphilis, chlamydia, and gonorrhea. These infections make it easier for HIV-1 to infect you.
 - o If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-1 negative.
 - o Get information and support to help reduce sexual risk behaviors.
 - o Do not miss any injections of APRETUDE. Missing injections increases your risk of getting HIV-1 infection.
 - o If you do become HIV-1 positive, you will need to take other medicines to treat HIV-1. APRETUDE is not approved for treatment of HIV-1.

If you have HIV-1 and receive only APRETUDE, over time your HIV-1 may become harder to treat.

What is APRETUDE?

APRETUDE is a prescription medicine used for HIV-1 PrEP to reduce the risk of getting HIV-1 infection in adults and adolescents who weigh at least 77 pounds (at least 35 kg). HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS). It is not known if APRETUDE is safe and effective in children younger than 12 years of age or weighing less than 77 pounds (less than 35 kg).

Do not receive APRETUDE if you:

- **already have HIV-1 infection.** If you are HIV-1 positive, you will need to take other medicines to treat HIV-1. APRETUDE is not approved for treatment of HIV-1.
- **do not know your HIV-1 infection status.** You may already be HIV-1 positive. You need to take other medicines to treat HIV-1. APRETUDE can only help reduce your risk of getting HIV-1 infection **before** you are infected.
- are allergic to cabotegravir.
- are taking any of the following medicines:

o carbamazepine	o phenytoin
o oxcarbazepine	o rifampin
o phenobarbital	o rifapentine

Before receiving APRETUDE, tell your healthcare provider about all your medical conditions, including if you:

- have ever had a skin rash or an allergic reaction to medicines that contain cabotegravir.
- have or have had liver problems.
- have ever had mental health problems.
- are pregnant or plan to become pregnant. It is not known if APRETUDE will harm your unborn baby. APRETUDE can remain in your body for up to 12 months or longer after the last injection. Tell your healthcare provider if you become pregnant while receiving APRETUDE.

Pregnancy Registry. There is a pregnancy registry for women who receive APRETUDE during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. It is not known if APRETUDE can pass to your baby in your breast milk. Talk with your healthcare provider about the best way to feed your baby while receiving APRETUDE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may interact with APRETUDE. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine. You can ask your healthcare provider or pharmacist for a list of medicines that interact with APRETUDE.

Do not start a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to receive APRETUDE with other medicines.

How will I receive APRETUDE?

- APRETUDE is initially given as an injection into the muscle of your buttock 1 time every month for the first 2 months, then as an injection 1 time every 2 months.
- Before receiving your first injection dose of APRETUDE, your healthcare provider may have you take 1 oral cabotegravir tablet 1 time a day for 1 month (at least 28 days). This will allow your healthcare provider to assess how well you will tolerate cabotegravir.
- APRETUDE is a long-acting medicine and may stay in your body for 12 months or longer after your last injection.
- Stay under the care of a healthcare provider while receiving APRETUDE. It is important that you receive APRETUDE as scheduled.
- If you miss or plan to miss a scheduled injection of APRETUDE by more than 7 days, call your healthcare provider right away to discuss your PrEP options.
- If you stop receiving APRETUDE, talk to your healthcare provider about other options to reduce the risk of getting HIV-1 infection.

What are the possible side effects of APRETUDE?

APRETUDE may cause serious side effects including:

- **Allergic reactions.** Call your healthcare provider right away if you develop a rash with APRETUDE. **Stop receiving APRETUDE and get medical help right away if you develop a rash with any of the following signs or symptoms:**

o fever

o blisters or sores in mouth

- o generally ill feeling
- o tiredness
- o muscle or joint aches
- o trouble breathing
- o blisters
- o redness or swelling of the eyes
- o swelling of the mouth, face, lips, or tongue

- **Liver problems.** Liver problems have happened in people with or without a history of liver problems or other risk factors. Your healthcare provider may do blood tests to check your liver function.

Call your healthcare provider right away if you develop any of the following signs or symptoms of liver problems:

- o your skin or the white part of your eyes turns yellow (jaundice)
- o dark or “tea-colored” urine
- o light-colored stools (bowel movements)
- o nausea or vomiting
- o loss of appetite
- o pain, aching, or tenderness on the right side of your stomach area
- o itching

- **Depression or mood changes. Call your healthcare provider or get emergency medical help right away if you have any of the following symptoms:**

- o feeling sad or hopeless
- o feeling anxious or restless
- o have thoughts of hurting yourself (suicide) or have tried to hurt yourself

The most common side effects of APRETUDE include:

- pain, tenderness, hardened mass or lump, swelling, bruising, redness, itching, warmth, loss of sensation at the injection site, abscess, and discoloration
- diarrhea
- headache
- fever
- tiredness
- sleep problems
- nausea
- dizziness
- passing gas
- stomach pain
- vomiting
- muscle pain
- rash
- loss of appetite
- drowsiness
- back pain
- upper respiratory infection

These are not all the possible side effects of APPRETUDE.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of APRETUDE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about APRETUDE that is written for health professionals.

What are the ingredients in APRETUDE?

Active ingredient: cabotegravir

Inactive ingredients: mannitol, polyethylene glycol (PEG) 3350, polysorbate 20, and Water for Injection.

Manufactured for:

ViiV Healthcare

Research Triangle Park, NC 27709

by:

GlaxoSmithKline

Research Triangle Park, NC 27709

APRETUDE is a trademark owned by or licensed to the ViiV Healthcare group of companies.

©2021 ViiV Healthcare group of companies or its licensor.

APR:1PIL

For more information, go to www.apretude.com or call 1-877-844-8872.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: December 2021

INSTRUCTIONS FOR USE

Apretude
(cabotegravir
extended-release
injectable suspension)

600 mg/3 mL
(200 mg/mL)

For gluteal intramuscular use only.

**600 mg/
3 mL Kit**

Overview:

A complete dose of APRETUDE requires 1 injection: 600 mg (3 mL) of cabotegravir. APRETUDE is a suspension that does not need further dilution or reconstitution. APRETUDE is for gluteal intramuscular use only.

Note: The ventrogluteal site is recommended.

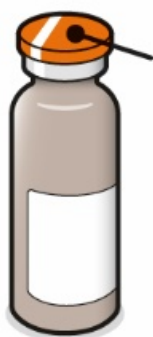
Storage information

Store at 2°C to 25°C (36°F to 77°F). Exposure up to 30°C (86°F) permitted.

Do not freeze.

Prior to administration:

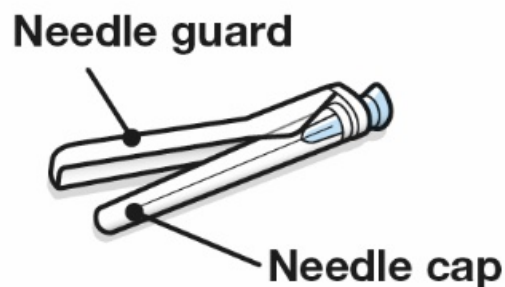
- If the pack has been stored in the refrigerator, the vial should be brought to room temperature prior to administration (not to exceed 30°C [86°F]).
- Once APRETUDE has been drawn into the syringe, the medication can remain in the syringe for up to 2 hours before injecting. The filled syringes should not be placed in the refrigerator. If the medicine remains in the syringe for more than 2 hours, the filled syringe and needle must be discarded.

APRETUDE vial

Vial cap
(Rubber stopper under cap)

Vial adapter**Syringe**

Plunger

Injection needle

Needle guard

Needle cap

Your pack contains:

- 1 vial of APRETUDE
- 1 vial adapter

- 1 syringe
- 1 injection needle (23 gauge, 1½ inch)
- Consider the individual's build and use medical judgment to select an appropriate injection needle length.

You will also need:

- Non-sterile gloves
- 2 alcohol wipes
- 2 gauze pads
- A suitable sharps container

Preparation:

1. Inspect the vial.

Check expiration date and medicine

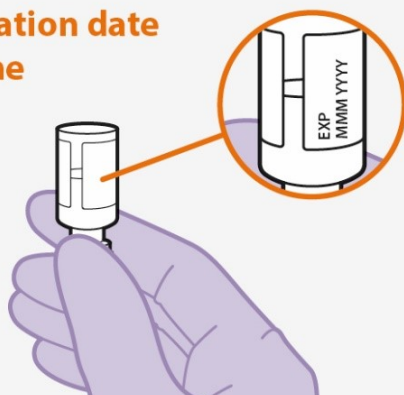


Figure A

- Check that the expiration date has not passed. **See Figure A.**
- Inspect the vial immediately. If you can see foreign matter, do not use the product.
Note: The vial has a brown tint to the glass.
- **Do not** use if the expiration date has passed.
- If the pack has been stored in the refrigerator, allow the medication to come to room temperature.

2. Shake the vial vigorously.

10 secs

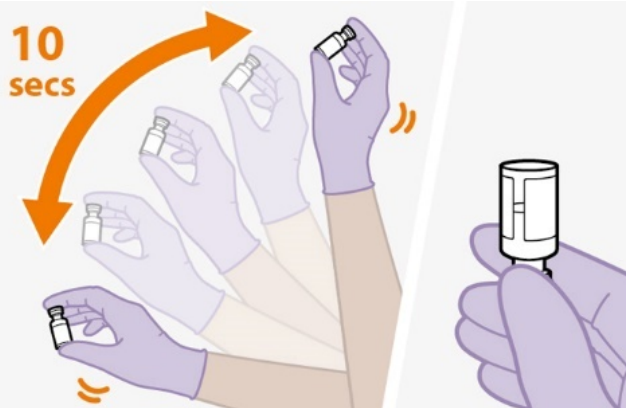


Figure B

- Hold the vial firmly, and vigorously shake for a full 10 seconds. **See Figure B.**
- Invert the vial and confirm the suspension is uniform. It should look uniform.
- If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.

3. Remove the vial cap.

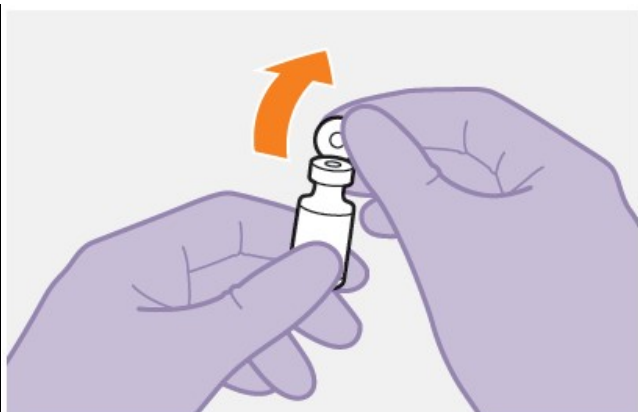


Figure C

- Remove the cap from the vial. **See Figure C.**
- Wipe the rubber stopper with an alcohol wipe.
Do not allow anything to touch the rubber stopper after wiping it.

4. Peel open the vial adapter.

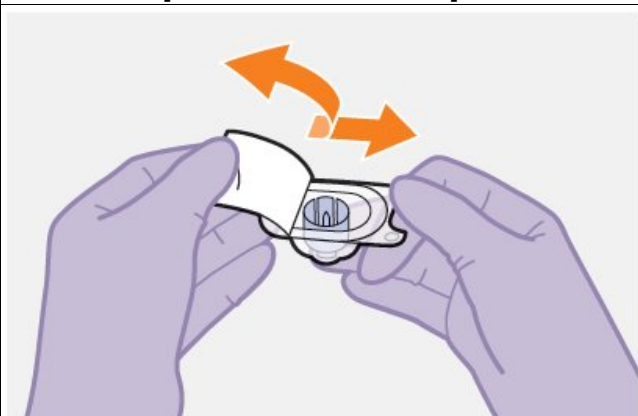


Figure D

- Peel off the paper backing from the vial adapter packaging. **See Figure D.**
Note: Keep the adapter in place in its packaging for the next step.

5. Attach the vial adapter.

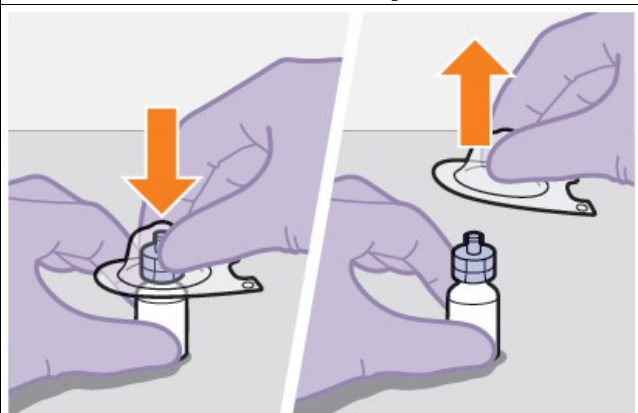


Figure E

- Press the vial adapter straight down onto the vial using the packaging, as shown. The vial adapter should snap securely into place.
- When you are ready, lift off the vial adapter packaging as shown. **See Figure E.**

6. Prepare the syringe.

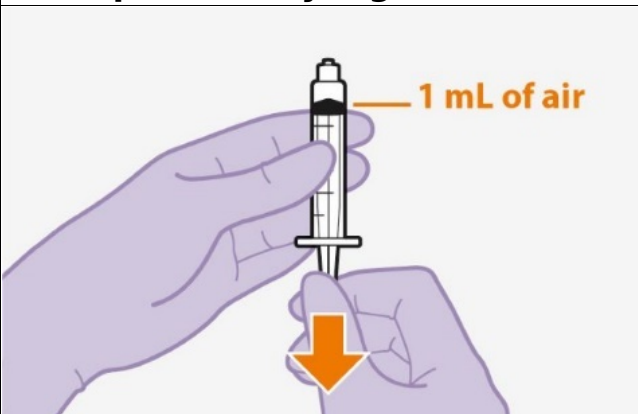


Figure F

- Remove the syringe from its packaging.
- Draw 1 mL of air into the syringe. This will make it easier to draw up the medicine later. **See Figure F.**

7. Attach the syringe.

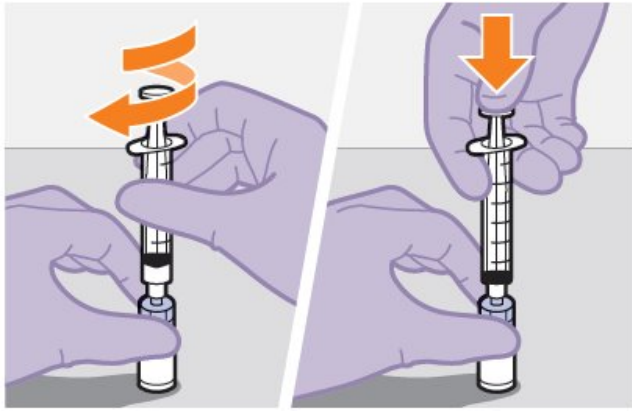


Figure G

- Hold the vial adapter and vial firmly, as shown.
- Screw the syringe firmly onto the vial adapter.
- Press the plunger all the way down to push the air into the vial. **See Figure G.**

8. Slowly draw up the dose.

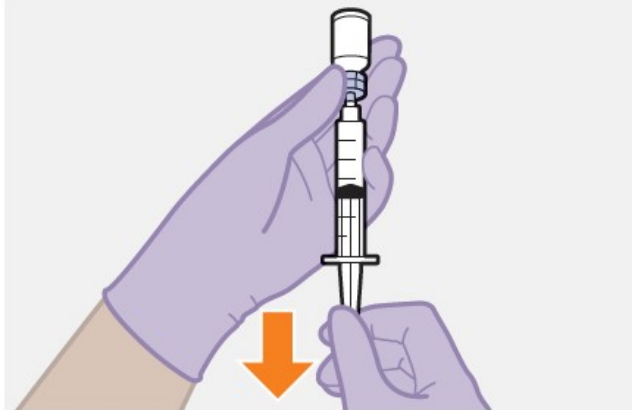


Figure H

- Invert the syringe and vial and slowly withdraw as much of the medicine as possible into the syringe. There may be more medicine than the dose amount. **See Figure H.**

9. Unscrew the syringe.

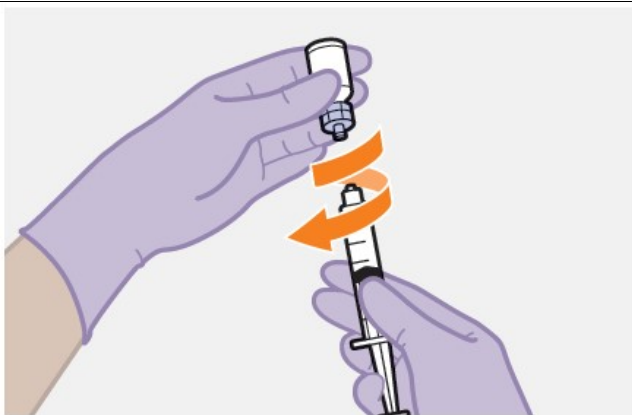
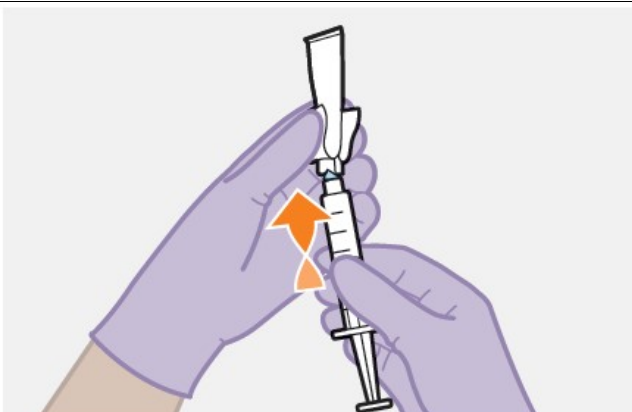


Figure I

- Unscrew the syringe from the vial adapter, holding the vial adapter as shown. **See Figure I.**
Note: Keep the syringe upright to avoid leakage. Check that the suspension looks uniform and milky white.

10. Attach the needle.



- Peel open the needle packaging part way to expose the needle base.
- Keeping the syringe upright, firmly twist the syringe onto the needle.
- Remove the needle packaging from the needle. **See Figure J.**

Figure J

Injection:

11. Prepare the injection site.

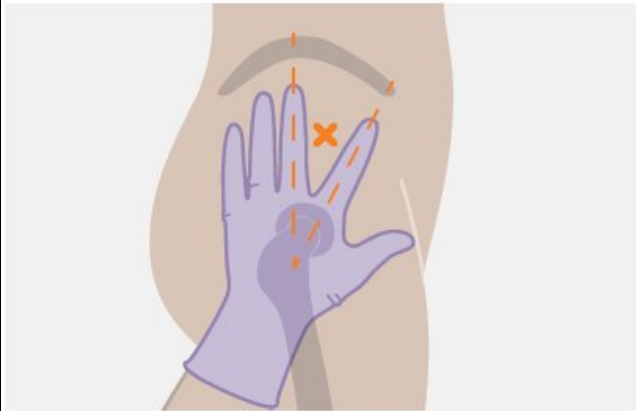


Figure K

APRETUDE must be administered to a gluteal site. **See Figure K.**

Select from the following areas for the injection:

- Ventrogluteal, as shown (recommended)
- Dorsogluteal, not shown (upper outer quadrant)

Note: For gluteal intramuscular use only. **Do not** inject intravenously.

12. Remove the cap.

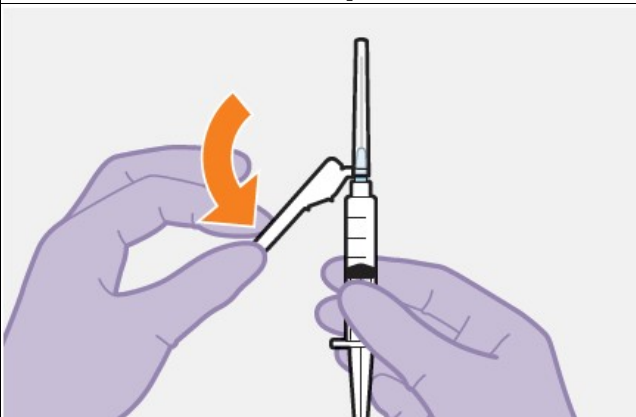


Figure L

- Fold the needle guard away from the needle. **See Figure L.**
- Pull off the injection needle cap.

13. Remove extra liquid from the syringe.

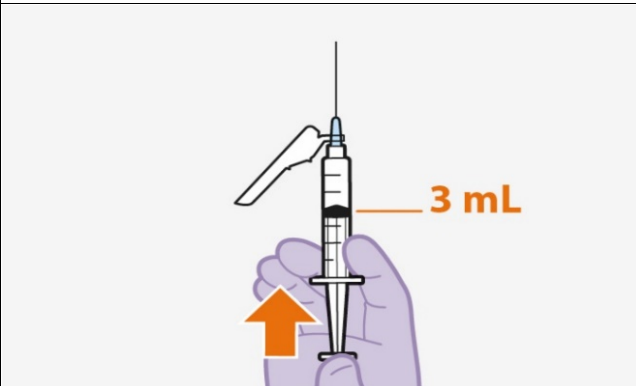


Figure M

- Hold the syringe with the needle pointing up. Press the plunger to the 3-mL dosing mark to remove extra liquid and any air bubbles. **See Figure M.**

Note: Clean the injection site with an alcohol wipe. Allow the skin to air dry before continuing.

14. Stretch the skin.



Figure N

Use the z-track injection technique to minimize medicine leakage from the injection site.

- Firmly drag the skin covering the injection site, displacing it by about an inch (2.5 cm). **See Figure N.**
- Keep it held in this position for the injection.

15. Insert the needle.

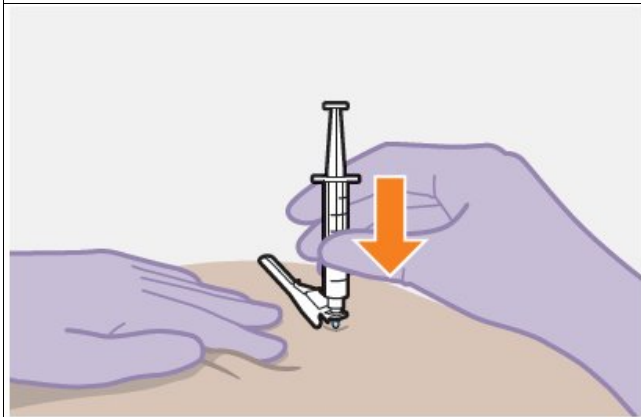


Figure O

- Insert the needle to its full depth, or deep enough to reach the muscle. **See Figure O.**

16. Inject the dose of medicine.

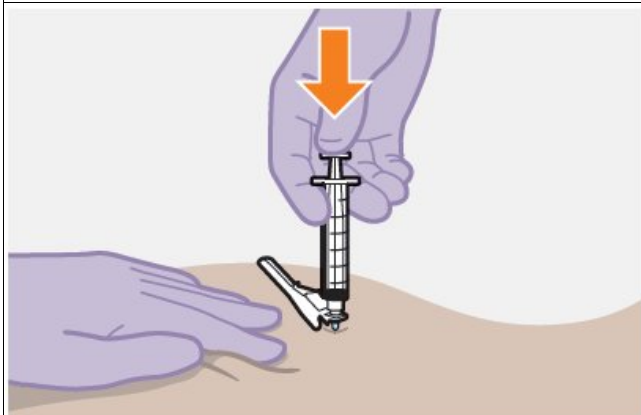


Figure P

- Still holding the skin stretched – slowly press the plunger all the way down. **See Figure P.**
- Ensure the syringe is empty.
- Withdraw the needle and release the stretched skin immediately.

17. Assess the injection site.

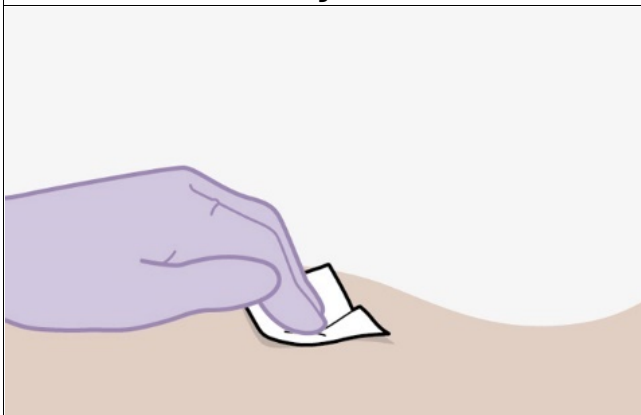


Figure Q

- Apply pressure to the injection site using a gauze pad. **See Figure Q.**
- A small bandage may be used if bleeding occurs.
Do not massage the area.

18. Make the needle safe.

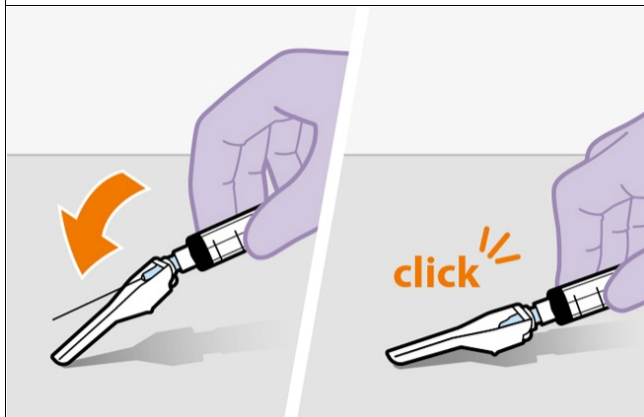


Figure R

- Fold the needle guard over the needle.
- Gently apply pressure using a hard surface to lock the needle guard in place.
- The needle guard will make a click when it locks. **See Figure R.**

After injection:

19. Dispose safely.



Figure S

- Dispose of used needle, syringe, vial, and vial adapter according to local health and safety laws. **See Figure S.**

Questions and Answers

1. If the pack has been stored in the refrigerator, is it safe to warm the vial up to room temperature more quickly?

The vial should be brought to room temperature before you are ready to give the injection, but make sure the vial does not get above 30°C (86°F).

Do not use any heating methods, other than using the warmth of your hands.

2. How long can APRETUDE be left in the syringe?

It is best to inject (room temperature) APRETUDE as soon as possible after drawing it up. However, APRETUDE can remain in the syringe for up to 2 hours before injecting.

If the medicine remains in the syringe for more than 2 hours, the filled syringe and needle must be discarded.

3. Why do I need to inject air into the vial?

Injecting 1 mL of air into the vial makes it easier to draw up the medicine into the syringe. Without the air, some liquid may flow back into the vial unintentionally, leaving less medicine than intended in the syringe.

4. Why is the ventrogluteal administration approach recommended?

The ventrogluteal approach into the gluteus medius muscle is recommended because it is located away from major nerves and blood vessels. A dorsogluteal approach into the gluteus maximus muscle is acceptable, if preferred by the healthcare professional. The injection should not be administered in any other site.

ViiV Healthcare
Research Triangle Park, NC 27709

GlaxoSmithKline
Research Triangle Park, NC 27709

APRETUDE is a trademark owned by or licensed to the ViiV Healthcare group of companies.

©2021 ViiV Healthcare group of companies or its licensor.

APR:2IFU

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: December 2021

Principal Display Panel

NDC 49702-264-23

Apretude

(cabotegravir extended-release injectable suspension)

600 mg/3 mL

(200 mg/mL)

Rx Only

For gluteal intramuscular use only.

Healthcare Professional Administration Only.

Contents:

1 Single-dose vial

1 Vial adapter

1 Syringe

1 Injection needle (23 gauge, 1 ½ inch)

Prescribing Information

Patient Information

Instructions for Use

ViiV Healthcare

600 mg/ 3 mL Kit

Made in Singapore

Rev. 12/21

©2021 ViiV Healthcare group of companies or its licensor.

62000000066159

NDC 49702-264-23

Rx Only



Apretude

(cabotegravir extended-release
injectable suspension)

600 mg/3 mL

(200 mg/mL)

For gluteal intramuscular use only.

Healthcare Professional Administration Only.



Contents:

1 Single-dose vial

1 Vial adapter

1 Syringe

1 Injection needle (23 gauge, 1½ inch)

Prescribing Information

Patient Information

Instructions for Use



OPEN HERE

**600 mg/
3 mL Kit**

APRETUDE

cabotegravir kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:49702-264
--------------	-------------------------	--------------------	---------------

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49702-264-23	1 in 1 CARTON; Type 0: Not a Combination Product	12/20/2021	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	3 mL

Part 1 of 1**CABOTEGRAVIR PREP**

cabotegravir injection, suspension, extended release

Product Information

Route of Administration	INTRAMUSCULAR
-------------------------	---------------

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CABOTEGRAVIR SODIUM (UNII: 3L12PT535M) (CABOTEGRAVIR - UNII:HMH0132Z1Q)	CABOTEGRAVIR	200 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
POLYSORBATE 20 (UNII: 7T1F30V5YH)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		3 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA215499	12/20/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA215499	12/20/2021	

Labeler - ViiV Healthcare Company (027295585)

Revised: 12/2021

ViiV Healthcare Company